

## **REMARKS**

Applicants respectfully request entry of the above amendments to the claims, and reconsideration of the application in light of the amendments to the claims and the arguments presented below.

Applicants thank the Examiner for acknowledging and entering the IDS submitted on March 1, 2007 along with the copies of cited references.

### **1. Claims Status**

The pending claims are set forth above. Claims 8-9 are currently pending. Claim 8 is currently amended. Support to current amendment is disclosed in the specification, as filed, on page 16. The amendments to the pending claims are made without prejudice or disclaimer, do not constitute amendments to overcome any prior art rejections under U.S.C. §§ 102 or 103, and are fully supported by the specification as filed. No new matter has been added as a result of the above amendments. The rejections set forth in the Office Action have been overcome by amendment or are traversed by argument below.

### **2. Withdrawn Rejections**

Applicants thank the Examiner for reconsidering and withdrawing rejection of claims 8 and 9 under 35 USC §112, first paragraph for lacking enablement for a reasonable number of therapeutically effective L1CAM antibodies; for withdrawing rejection of claims 8 and 9 under 35 USC §102(b) in view of Hoefnagel et al., in view of Carrel et al. and Mujoo et al.; and for withdrawing rejection of claims 8 and 9 under 35 USC §103 over Wolff et al. in view of Cleland et al.

### **3. Claim Rejections 35 USC §112**

A) The Office has maintained rejection of claims Claims 8 and 9 as being rejected under 35 USC §112, first paragraph for lacking enablement for using any L1CAM antibody to inhibit proliferation of any cancer cell. The Office Action continues to assert that the specification does not provide reasonable enablement for specific, site-directed accumulation of the anti-L1CAM antibody or binding-fragment thereof to just any cancer with the intention of treating cancer on the basis that the delivery of high molecular weight molecules such as antibodies to cancers in vivo is unpredictable. The

Action further asserts that at the time of filing of application, only a limited number of monoclonal antibodies were FDA approved for clinical use, and of those, even fewer were intended for cancer therapy. The Action cites teachings of Reichert et al (Nat. Biotech. 23(9): 1073-1078) especially Table 1 together with previously cited Arlt et al. and currently cited Izumoto et al. (Can. Res. 56: 1440-1444, 1996) to support its argument. Applicants traverse this rejection.

As discussed in their previous response, Applicants submit that the art of drug delivery has made significant advancement. At the time of filing of instant application (October 2003) antibody/drug delivery was a well established art, as is evident by disclosure in specification on paragraph [0012] where Applicants discuss successful use of a monoclonal antibody (Herceptin®) against Her2/Neu for treatment of breast cancer. In addition, one of the references cited in the previous Action, Hoefnagel et al., (published in 2001) itself provides a method to successfully delivering <sup>131</sup>I-conjugated L1CAM antibodies to xenografts in mice.

According to MPEP 2164.01, paragraph 3, *"The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation."*

Applicants respectfully submit that the specification discloses *in vitro* experiments that show inhibition of growth of cancer cells expressing L1CAM. Furthermore, the specification teaches method for administration of L1CAM antibodies or fragments thereof in paragraph [0043] to [0048] and [0055]. In addition, *in vitro* experimentation has become a conventional method to find successful agents for cancer treatment. Therefore, Applicants are not required to provide the type of evidence required, *inter alia*, by the Food and Drug Administration for approval of a new drug. Applicants can fulfill the requirements of 35 U.S.C. 112, first paragraph by showing said antibodies work in an acceptable *in vitro* model system, and thus that administration to humans or animals for cancer treatment can be performed without undue experimentation.

With respect to the argument presented in the Action in view of Reichert et al. (Nat. Biotech. 23(9): 1073-1078) that only a limited number of monoclonal antibodies are approved by FDA and therefore success of L1CAM antibodies in clinic is unpredictable, Applicants respectfully submit that this fact improperly implicates the standards of FDA approval rather than patentability. The success of Applicants' *in vitro* model is predictive for success with regard to the claimed pharmaceutical

composition. Furthermore, the Reichert reference itself states (on page 1073, paragraph 1) that monoclonal antibodies now comprise the **majority** of recombinant proteins currently used clinically, and that monoclonal antibodies have a higher probability of approval success than small molecule drugs. The reference continues (paragraph 2 on page 1073) that approval success rates for chimeric and humanized monoclonal antibodies are consistently 18-29%. The cited reference further states that most monoclonal antibodies studied were for treatment of oncological and immunological indications and FDA approved antibodies in these two categories comprise 89% of total approved monoclonal antibodies (page 1076, paragraph 2). Applicants therefore submit that even the teachings in Reichert et al. support Applicants' claim to pharmaceutical composition to treat tumor expressing L1CAM.

In an effort to expedite prosecution, Applicants have amended claim 8 add limitation of "humanized". Support for the amendment can be found in the original disclosure on page 16, line 4.

Based on the arguments presented above, Applicants request the Examiner to reconsider and withdraw the rejection under 35 USC §112, first paragraph.

B) The Office rejected claim 8 under 35 US § 112, first paragraph for failing to comply with the written description requirement in view of the amendment made to the claim, which are asserted in the Action to comprise new matter. Without acquiescing to the correctness of these assertions, Applicants have amended the claim to remove the negative limitation thereby overcoming this ground of rejection.

#### **4. Claim Rejections under 35 USC §102(b)**

Claims 8 is rejected under 35 US § 102 (b) as being anticipated in view of Izumoto et al. The Action further states that Izumoto teaches inhibition of L1-mediated cell migration of rat C6 glioma by rabbit anti-rat L1 antibodies. Applicants traverse this rejection.

According to M.P.E.P. §2131, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Applicants respectfully submit the claim as currently amended teaches the use of unconjugated humanized anti-L1CAM antibody or L1CAM-binding fragment thereof to inhibit proliferation of a tumor cell of neurological origin. The cited reference does not teach humanized antibodies, nor does it teach that anti-L1CAM antibodies can be used to inhibit tumor cell proliferation. Thus, the cited reference does not teach each and every limitation of pending claim and cannot anticipate said claim.

Applicants respectfully request the Examiner to reconsider and withdraw rejection of claim under 35 US § 102 (b) in view of Applicants' amendments and arguments submitted herewith.

#### **5. Claim Rejections 35 USC §103(a)**

Claim 8 is rejected under 35 USC §103(a) as being obvious over Rathjen et al (EMBO J., 3: 1-10, 1984), in view of Cleland et al. (J. Pharm. Sci., 90: 310-321, 2001). Applicants traverse this rejection.

In order to establish a *prima facie* case of obviousness the Patent office must establish: 1) a teaching, suggestion or motivation found within the prior art or within the knowledge of one of skill in the art to combine or modify the references; and 2) a reasonable expectation of success. The prior art references (alone or in combination) must teach or suggest *all* the claim limitations. MPEP § 706.02(j).

The combination of Rathjen et al. and Cleland et al. does not teach or suggest at least the following limitations of currently amended claim 8:

"A pharmaceutical composition for treating a tumor by inhibiting proliferation of a tumor cell of neurological origin that expresses L1CAM, wherein the composition comprises an unconjugated humanized anti-L1CAM antibody or L1CAM-binding fragment thereof..... ."

As discussed in previous response to Office Action, Rathjen et al. does not provide any reason for the skilled worker to use an unconjugated anti-L1CAM antibody or L1CAM-binding fragment for inhibiting tumor cell proliferation. Cleland et al. does not cure this deficiency, because it also does not teach this use of an unconjugated anti-L1CAM antibody or L1CAM-binding fragment. Specifically, Cleland et al. merely teaches excipients for stabilizing a monoclonal HER2 antibody.

Based on this significant difference between current invention and combined teachings of the cited art, Applicants respectfully submit that the combination of Rathjen et al. and Cleland et al. does not render the instant claim obvious.

Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

### **CONCLUSIONS**

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If the Examiner believes it to be helpful, he is invited to contact the undersigned representative by telephone at 312-913-0001.

Respectfully submitted,

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